EXHIBIT 1, Tab 11

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The Effectiveness of Early Treatment with "Second-Line" Antirheumatic Drugs

A Randomized, Controlled Trial

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Objective: To compare two therapeutic strategies for patients with recent-onset rheumatoid arthritis.

Design: Open, randomized clinical trial.

Setting: Outpatient clinics of six clinical centers.

Patients: 238 consecutive patients with recently diagnosed rheumatoid arthritis.

Interventions: Delayed or immediate introduction of treatment with slow-acting antirheumatic drugs (SAARDs).

Measurements: Primary end points were functional disability, pain, joint score, and erythrocyte sedimentation rate at 6 and 12 months and progression of radiologic abnormalities at 12 months.

Results: Statistically significant advantages at 12 months for patients receiving the SAARD strategy (immediate treatment with SAARDs) with regard to all primary end points that may be clinically important are indicated by the differences in improvements from baseline and their 95% CIs. These differences were 0.3 (95% CI, 0.2 to 0.6) for disability (range, 0 to 3), 10 mm (CI, 1 to 19 mm) for pain (range, 0 to 100 mm), 39 (CI, 4 to 74) for joint score (range, 0 to 534), and 11 mm/h (CI, 3 to 19 mm/h) for erythrocyte sedimentation rate (range, 1 to 140 mm/h), all in favor of SAARD treatment. The SAARD strategy also appears to be advantageous at 6 months. Radiologic abnormalities progressed at an equal rate in the SAARD and the non–SAARD groups; the difference in progression (range, 0 to 448) was 1 (CI, −3 to 5). Analyses were based on the intention-to-treat principle and thus included 29% of patients in the non–SAARD group who discontinued the non–SAARD treatment strategy; treatment was usually discontinued because of insufficient effectiveness. The SAARD strategy including two alternative SAARDs could not be continued by 8% of patients, usually because of adverse reactions.

Conclusions: Early introduction of SAARDs may be more beneficial than delayed introduction for patients with recently diagnosed rheumatoid arthritis.

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In recent years, therapeutic strategies for patients with rheumatoid arthritis have been discussed in detail (1–8). Traditional therapy, usually referred to as the "pyramid model," begins with nonsteroidal anti-inflammatory drugs (NSAIDs). If these are insufficiently effective, they are later replaced or supplemented with second-line antirheumatic drugs, which are distinguished from NSAIDs primarily by their assumed disease-modifying potential and delayed onset of action. These second-line drugs are also referred to as slow-acting antirheumatic drugs (SAARDs) or disease-modifying antirheumatic drugs (DMARDs). Traditionally, the SAARDs of first choice have been hydroxychloroquine or intramuscular gold followed by D-penicillamine, methotrexate, or azathioprine. The traditional therapeutic pyramid is based on the principle of "primum non nocere": Because of their potential toxicity, SAARDs should only be given when "milder" therapies have failed.

Recently, the beneficial effects of the pyramid strategy have been questioned because the long-term outcome of rheumatoid arthritis continues to be disappointing. Patients with rheumatoid arthritis have increased mortality (9, 10), and their quality of life is seriously affected by functional impairment and loss of employment (11, 12). The pyramid model might be undesirable because administering SAARDs only after milder regimens prove to be insufficiently effective delays the suppression of inflammation. It is preferable that the disease process be controlled as soon as possible, because radiologic abnormalities appear in the joints early in the course of the

See editorial comment on pp 773-774.

disease (13, 14) and are related to the extent of inflammation (15, 16). Toxicity indices for NSAIDs and most SAARDs have recently been shown to be similar; thus, exposure of patients to possible adverse reactions is probably not in itself a reason to withhold treatment with SAARDs (17).

However, the ability of SAARDs to modify the course of disease and prevent radiologic damage is often questioned (18, 19). The poor long-term outcome of rheumatoid arthritis might be caused not by a delay in effective treatment but by the low disease-modifying power of both first- and second-line drugs. The short courses of SAARDs (short because of adverse reactions or impatience with a delay in effect) might also play a role (20, 21). Combinations of SAARDs have not been shown to be superior to single drugs (21, 22).

Current clinical practice is shifting toward the earlier introduction of second-line treatment for rheumatoid arthritis, but thus far no clinical trials have shown this strategy to be beneficial. We investigated the consequences of ignoring the treatment pyramid for patients with recent-onset rheumatoid arthritis. In this report, we describe the first-year results of a randomized clinical trial in which the delayed and the immediate introduction of SAARDs were compared. Effectiveness was measured by disease activity and progression of radiologic abnormalities. The various SAARDs are considered as a single group in this report; comparisons among the second-line therapies will be reported in detail later.

Methods

Patients

As of January 1990, all patients with recent-onset rheumatoid arthritis (diagnosed according to the 1987 American College of Rheumatology criteria [23]) from six rheumatologic centers in the region of Utrecht, the Netherlands, were asked to participate in a randomized, prospective clinical trial. Disease duration had to have been less than 1 year, and most patients were enrolled shortly after diagnosis. The following exclusion criteria were applied: 1) age younger than 17 years, 2) comorbid conditions that might interfere with one of the therapeutic strategies, 3) previous or current treatment with any SAARDs, glucocorticosteroids, or cytotoxic or immunosuppressive therapy, 4) the possibility of pregnancy or breast feeding, and 5) psychiatric or mental disturbances that would make adherence to the study protocol unlikely. All patients gave informed consent before study entry and were told that the study was intended to compare the unsure outcome of treatment with NSAIDs alone with that of treatment with NSAIDs and a SAARD for rheumatoid arthritis at an early stage. The study design was approved by the ethical committees of all participating hospitals.

The baseline characteristics of patients who were eligible for the study but who objected to randomization were compared with those of randomly assigned patients to determine whether any selection bias had occurred.

Treatment

Patients entering the study were randomly assigned to one of two therapeutic groups. All randomization procedures were done by drawing sealed envelopes from blocks of 100 with equal numbers of patients for each of the four treatments per hospital; the person doing the procedures was blinded to treatment assignments. This method was used because eligible patients were not distributed equally among the centers. The assigned therapeutic strategy was continued for at least 1 year.

In the non–SAARD group, patients began receiving NSAID therapy, the dose and type of which could be modified at any time. For this group, initiation of SAARD treatment during the study was regarded as discontinuation of the therapeutic strategy. In the SAARD group, patients were randomly assigned (by persons blinded to treatment assignments) to treatment with one of the following SAARDs: hydroxychloroquine (400 mg/d), intramuscular gold (aurothioglucose, 50 mg/wk), or oral methotrexate (7.5 to 15 mg/wk). Therapy with the initial SAARD was continued for 12 months unless adverse reactions necessitated discontinuation; if this occurred, another SAARD was given. Hydroxychloroquine was followed by auranofin (6 to 9 mg/d); intramuscular gold was followed by D-penicillamine (500 to 750 mg/d); and methotrexate was followed by sulfasalazine (2000 to 3000 mg/d). Discontinuation of therapy with the second SAARD was regarded as discontinuation of the therapeutic strategy. Use of NSAIDs was allowed in the SAARD group; as in the non–SAARD group, the dose and type could be changed at any time. Patients were assigned to the non–SAARD group and the SAARD group in a ratio of 1:3, and power calculations for the primary end point disability ($\alpha = 0.05$; $\beta = 0.20$; difference to be detected, 25%) indicated that group sizes of 40 and 120, respectively, would be sufficient. The ratio of 1:3 was chosen to enable later comparisons of results within the SAARD group, which were thought to be similar. The use of analgesics was allowed in both groups; the use of oral glucocorticosteroids was avoided if possible; and intra-articular injections were not allowed within 2 months of a scheduled visit.

Criteria for discontinuation or dose adjustment of a SAARD because of adverse reactions were

described in detail in the study protocol. Discontinuation of any treatment because of sustained disease activity was done only if the patient and the attending physician (who had to discuss the patient with a colleague) judged it to be unavoidable.

Primary End Points

Assessments were done at the start of the trial and were repeated every 3 months. Clinical variables were assessed by the same physician or research nurse for each patient on each occasion. Primary end points were functional disability, pain, joint score, erythrocyte sedimentation rate, and radiologic abnormalities (24). Radiologic abnormalities and erythrocyte sedimentation rate were determined by persons blinded to treatment assignments; functional disability and pain were self-assessed scores; and determination of the joint score was not blinded to treatment. Functional disability was assessed using a validated Dutch version of the Health Assessment Questionnaire Disability Score (25–27). The questionnaire scores range from 0 to 3; 0 is the best score (no problems), and 3 is the worst. Pain was measured on two horizontal visual analog scales of 100 mm; the mean of the scores for pain during the night and pain during the morning was calculated. The joint score according to Thompson and colleagues (28, 29) assessed the simultaneous presence of joint tenderness and swelling in a selection of joints weighed for joint size (range, 0 to 534) (28, 29). Erythrocyte sedimentation rate (mm/h) was measured using Westergren method. Radiography of hands and feet was done at the start of the study and at 12 months. A modified version of the method of Sharp and coworkers (30, 31) was used to score radiologic abnormalities. According to this method, erosions and joint space narrowing in hand and foot joints are scored and added together to obtain a total radiologic damage score (range, 0 to 448). All radiographs were evaluated by two investigators who were blinded to treatment assignments. The scores of the first investigator were used in the analyses, and the scores of the second investigator were used to validate the scores of the first. Correlation between the two sets of scores was satisfactory (Spearman correlation coefficients for scores at baseline and at 12 months were 0.84 for both); the second investigator was found to have given lower scores (means at baseline were 4.2 and 3.4, respectively; means at 12 months were 11.2 and 9.7, respectively). Therefore, in individual cases, differences in total scores of 25% or more were discussed until an agreement was reached on the appropriate score. That score was then used in the analyses.

Additional Assessments

Secondary end points were grip strength (mean of three measurements of each hand with a vigorimeter [Martin, Tuttlingen, Germany] in kPa), duration of morning stiffness (maximum, 720 min), and general well-being (horizontal visual analog scale of 100 mm). Additional laboratory variables were serum level of C-reactive protein (mg/L), hemoglobin concentration (mmol/L), and platelet count ($\times 10^9$/L).

Rheumatoid factor status was determined to be positive or negative, as indicated by either the Latex fixation test or the Rose–Waaler test. Adverse reactions to medication were registered in detail as reported by patients or indicated by laboratory test results.

Statistical Analysis

The intention-to-treat principle was applied. At 6 and 12 months, changes from baseline values were calculated for all end points. Measures of effect were point estimates of the differences in mean change between the non–SAARD group and the SAARD group and the accompanying 95% CIs. Nonparametric statistical significance tests (Mann–Whitney U tests) of differences in change were also applied but did not alter the results. Clinically significant improvement in primary end points for individual patients was defined before the data analysis was begun as an improvement of 33% or more compared with baseline (32). Patients were considered to have had a complete response when the duration of morning stiffness was less than 15 minutes, the mean pain score was less than 10 mm, the joint score was less than 10, and the erythrocyte sedimentation rate was less than 30 mm/h (this is a modified version of the definition of complete response by Scott and coworkers [33]). No adjustments were made for multiple comparisons (34). Statistical analyses were done using the SPSS/PC+ statistical package (SPSS Inc., Chicago, Illinois) (35).

Results

Patient Characteristics

In April 1994, 238 patients enrolled in the study had each had at least 12 months of follow-up. These patients were the subject of this study.

Data on 18 patients (3 from the non–SAARD group and 15 from the SAARD group) who were randomly assigned to treatment and were entered into the study but who were then lost to follow-up were not included in any of the analyses. Five of these patients died of causes unrelated to rheumatoid arthritis or its treatment; another 5 were excluded from the study because of serious disease

Table 1. Baseline Characteristics*

Variable (Unit)†	Non–SAARD Group (n = 57)	SAARD Group (n = 181)	Dropouts (n = 18)	Patients Who Were Not Randomly Assigned (n = 55)
Female sex, %	70	68	39	76
Rheumatoid factor–positive, %	59	63	61	71
Age, *y*				
Mean	56	57	66	55
Median	60	58	73	58
10th–90th percentiles	31–72	38–74	45–78	33–72
Primary end points				
Disability score				
Mean	1.3	1.3	1.8	1.0
Median	1.4	1.3	2.2	0.9
10th–90th percentiles	0.5–2.3	0.3–2.4	0.1–2.8	0–2.1
Pain score, *mm*				
Mean	45	44	41	33
Median	44	45	31	29
10th–90th percentiles	8–88	5–86	7–94	1–74
Joint score				
Mean	136	142	145	126
Median	119	116	136	101
10th–90th percentiles	20–319	45–285	37–233	24–260
Erythrocyte sedimentation rate, *mm/h*				
Mean	42	41	41	42
Median	37	35	28	34
10th–90th percentiles	8–82	11–85	13–88	7–92
Radiologic damage score‡	5	4	2	5
Mean	5	4	2	5
Median	2	2	2	3
10th–90th percentiles	0–15	0–12	0–4	0–15
Secondary end points				
Grip strength, *kPa*				
Mean	31	30	21	34
Median	27	27	18	32
10th–90th percentiles	8–60	3–58	1–43	7–61
Well-being score, *mm*				
Mean	52	48	51	40
Median	50	50	50	36
10th–90th percentiles	12–92	10–83	17–93	2–85
Morning stiffness, *min*				
Mean	87	111	86	89
Median	60	60	30	60
10th–90th percentiles	4–180	4–240	0–194	0–180
C-reactive protein level, *mg/L*§				
Mean	32	34	27	27
Median	25	17	22	20
10th–90th percentiles	0–86	0–85	6–67	0–70
Hemoglobin concentration, *mmol/L*				
Mean	7.9	7.9	8.0	7.7
Median	8.1	7.9	8.2	7.5
10th–90th percentiles	6.5–8.9	6.8–9.0	6.6–9.2	6.1–9.3
Platelet count, $\times 10^9$/*L*				
Mean	347	344	337	352
Median	317	321	347	318
10th–90th percentiles	235–560	216–495	213–435	254–561

* Higher values indicate more active disease, with the exception of values for grip strength and hemoglobin level. SAARD = slow-acting antirheumatic drugs.
† Ranges for variables are as follows: disability score, 0 to 3; pain score, 0 to 100 mm; joint score, 0 to 534; erythrocyte sedimentation rate, 1 to 140 mm/h; radiologic damage score, 0 to 448; grip strength, 0 to 120 kPa; well-being score, 0 to 100 mm; morning stiffness, 0 to 720 min.
‡ The numbers of patients tested were 44 in the non–SAARD group, 136 in the SAARD group, 13 of the study dropouts, and 48 persons who were not randomly assigned to treatment.
§ The numbers of patients tested were 44 in the non–SAARD group, 124 in the SAARD group, 16 of the study dropouts, and 45 persons who were not randomly assigned to treatment.

processes other than rheumatoid arthritis (4 had cancer and 1 had a cerebrovascular hemorrhage). In 2 patients, the diagnosis of rheumatoid arthritis was incorrect (both patients received a diagnosis of polymyalgia rheumatica). Six patients (all from the SAARD group) refused to follow the study protocol because of anxiety or because the medication was ineffective.

Of the 238 patients, 57 were randomly assigned to the non–SAARD strategy group, and 181 were randomly assigned to the SAARD strategy group. The baseline characteristics of all patients are given in Table 1. The male to female ratio was typical for a population of patients with rheumatoid arthritis, and the percentage of patients positive for rheumatoid factor was also not atypical. Mean age in both patient groups was high for patients with recent-onset rheumatoid arthritis. Variables of disease status at the start of the study were similar for the non–SAARD and SAARD groups. Radiographs were available for 44 patients in the non–SAARD group and 136 patients in the SAARD group; C-

reactive protein levels were not determined quantitatively in all participating hospitals and were therefore missing in several cases.

The baseline characteristics of 18 patients lost to follow-up were generally similar to those of patients in the therapeutic groups, except that the patients lost to follow-up were more often male and were slightly older. Patients who did not agree to randomization ($n = 55$) tended to have slightly better baseline values, with the exception of values for the laboratory variables.

Discontinuation of Therapeutic Strategies

Table 2 shows the numbers of patients whose assigned therapeutic strategies were discontinued. In both 6-month periods, discontinuation occurred more frequently in the non–SAARD group: Twenty-nine percent of 57 patients who completed follow-up could not continue to receive the non–SAARD therapeutic strategy for 1 year. Discontinuation was usually done because NSAID therapy was insufficiently effective. In Table 2, discontinuation of the SAARD strategy implies discontinuation of therapy with a second SAARD, an event that occurred in 8% of patients. The SAARD therapies were usually stopped because of adverse reactions. Other than adverse reactions or ineffectiveness, the reason for discontinuation was a diagnosis of Wegener disease. In the SAARD group, 81% of patients were still using the first SAARD at the end of the study year.

Corticosteroids

The decision to administer either oral or intra-articular steroids was made by clinicians who were not blinded to treatment assignments. Oral corticosteroids were used in similar percentages of patients in both study groups: 12% of patients in the non–SAARD group and 9% of patients in the SAARD group after 1 year (Table 3). Intra-articular injections were given more frequently in the non–SAARD group: They were given to 26% of patients in the non–SAARD group and only 11% of patients in the SAARD group during the first 6 months and to 40% of patients in the non–SAARD group and only 19% of patients in the SAARD group during 12 months. Joints that had received an injection less than 2 months before an evaluation were not included in the joint score. Injections were not given within 1 month before the 6- or 12-month assessments of disease activity.

Effectiveness

The effectiveness of the two therapeutic strategies is presented in Table 4. Statistically significant advantages at 12 months for the SAARD strategy for disability, pain, joint score, and erythrocyte sedimentation rate (which may be clinically important) are indicated by the differences in improvements from baseline and their 95% CIs. The SAARD strategy also appears to have been advantageous at 6 months. An increase in radiologic damage during the first year of disease was similar in both treatment groups ($P > 0.50$). Missing values on radiologic deterioration were primarily due to unfamiliarity with the study protocol in an early phase of the study and were distributed equally between both groups. Disease activity values in patients without radiologic scores were slightly worse than values in patients who had such scores, but they were similar in both groups. To find out whether the relatively frequent discontinuation of the therapeutic strategy in the non–SAARD group affected the estimation of the difference in effect, we compared the changes found for "continuers" and "noncontinuers" from the non–SAARD group, even though the numbers of patients in these subgroups were small. The noncontinuers improved statistically significantly more (data not shown) than the continuers according to all primary end points at 6 months ($n = 10$ and $n = 47$, respectively) and 12 months ($n = 16$ and $n = 41$, respectively). Radiologic damage was an exception to this; it increased similarly in both groups. Thus, it seems likely that discontinuation in the non–

Table 2. Numbers of Patients Whose Assigned Strategies Were Discontinued and Reasons for Discontinuation*

Period	Treatment Group	Patients Who Discontinued Strategy, *n* (%)	Reason for Discontinuation		
			Adverse Reactions	Ineffectiveness	Other
			Patients, *n*		
0 to 6 months	Non–SAARD	10 (18)†	0	10	0
	SAARD	4 (2)‡	3	1	0
6 to 12 months	Non–SAARD	6 (11)†	0	5	1
	SAARD	11 (6)‡	9	2	0
0 to 12 months	Non–SAARD	16 (29)†	0	15	1
	SAARD	15 (8)‡	12	3	0

* SAARD = slow-acting antirheumatic drugs.
† Patients received follow-up therapy with a SAARD
‡ Patients received follow-up therapy with a SAARD other than the one to which they were originally assigned

Table 3. Use of Oral or Intra-articular Corticosteroids*

Period	Non–SAARD Group (n = 57)	SAARD Group (n = 181)
	Patients, n (%)	
Oral corticosteroids		
0 to 6 months	4 (7)	11 (6)
0 to 12 months	7 (12)	16 (9)
Intra-articular corticosteroids		
0 to 6 months	15 (26)	19 (11)
0 to 12 months	23 (40)	35 (19)

* SAARD = slow-acting antirheumatic drugs.

SAARD group caused the estimated difference in main effect to be conservative.

In Table 5, secondary end points are shown to be consistent with the results presented in Table 4. All end points favor the SAARD strategy at 6 and 12 months. The percentages of patients showing clinical improvement (≥33% of baseline value) in primary end points at 6 months varied from 27% (for disability) to 51% (for joint score) in the non–SAARD group and from 44% (for disability) to 67% (for joint score) in the SAARD group. At 12 months, these percentages varied from 28% (for disability) to 57% (for joint score) in the non–SAARD group and from 54% (for disability) to 78% (for joint score) in the SAARD group. Thus, at 6 months, the percentage of improved patients was 16% to 21% higher in the SAARD group; at 12 months, this percentage was 19% to 26% higher in the SAARD group. All differences were statistically significant. Complete response was achieved in 11% of patients in the non–SAARD group and 24% of patients in the SAARD group at 12 months.

Adverse Reactions

In the non–SAARD group, 16 patients (28%) reportedly had serious gastrointestinal symptoms. One had a gastrointestinal hemorrhage, and 7 reported headaches, dizziness, or concentration problems. Other adverse reactions were rare.

Major adverse reactions leading to the discontinuation of SAARD therapy primarily consisted of gastrointestinal symptoms (in 9 patients [16%]) and skin reactions (in 7 patients [12%]). All adverse reactions necessitating discontinuation were reversible. Anxiety about adverse reactions was a reason for discontinuation in 4 patients. Relatively rare reasons for SAARD discontinuation were increased aminotransferase levels (2 patients), headaches or concentration problems (2 patients), proteinuria (1 patient), herpes zoster infection (1 patient), pneumonitis (1 patient), and mouth ulcers (1 patient). Mild toxicity, which did not lead to the discontinuation of therapy, was frequent and was evident primarily as gastrointestinal symptoms (64 patients had such symptoms; in 37 of these patients, symptoms were attributed to use of NSAIDs), skin reactions (17 patients), headache or dizziness (15 patients; in 4 of these patients, symptoms were attributed to use of NSAIDs), oral mucosal erosions (10 patients), increased transaminase levels (9 patients), upper respiratory tract infections (8 patients), hair loss (6 patients), thrombopenia or leukopenia (5 patients), dyspnea (4 patients), proteinuria (3 patients), or increased serum creatinine concentrations (2 patients; in 1 patient, the increase was attributed to use of NSAIDs).

Discussion

In this open randomized study, we compared therapeutic strategies rather than individual drugs in patients who had recently received a diagnosis of rheumatoid arthritis. Early second-line treatment appears to have important advantages over a therapeutic strategy in which the introduction of SAARDs is postponed, such as the traditional pyramid strategy. Important and sensitive end points, such as disability and pain, and measures of the disease process, such as joint score and erythrocyte sedimentation rate, improved statistically significantly more in the SAARD group than in the non–SAARD group during the study year. Radiologic progression, however,

Table 4. Changes from Baseline in the Non–SAARD Group and the SAARD Group: Primary End Points*

Primary End Points	Non–SAARD Group† (n = 57)	SAARD Group† (n = 181)	Difference‡
6 months			
Disability score	0.0 (−0.7, 0.7)	−0.3 (−0.9, 0.3)	0.3 (0.1 to 0.5)
Pain score, *mm*	−15 (−44, 14)	−20 (−47, 7)	5 (−3 to 14)
Joint score	−34 (−178, 110)	−74 (−184, 37)	40 (−2 to 82)
Erythrocyte sedimentation rate, *mm/h*	−5 (−33, 23)	−16 (−39, 7)	11 (4 to 19)
12 months			
Disability score	−0.1 (−0.8, 0.6)	−0.4 (−1.0, 0.2)	0.3 (0.2 to 0.6)
Pain score, *mm*	−11 (−43, 21)	−21 (−49, 7)	10 (1 to 19)
Joint score	−50 (−185, 85)	−89 (−199, 21)	39 (4 to 74)
Erythrocyte sedimentation rate, *mm/h*	−5 (−32, 22)	−16 (−41, 9)	11 (3 to 19)
Radiologic damage score§	+8 (0, 21)	+7 (0, 18)	1 (−3 to 5)

* Ranges for end point variables are as follows: disability score, 0 to 3; pain score, 0 to 100 mm; joint score, 0 to 534; erythrocyte sedimentation rate, 1 to 140 mm/h; radiologic damage score, 0 to 448. SAARD = slow-acting antirheumatic drugs.
† Values are the mean (−SD, +SD). Negative values indicate improvement for all end points.
‡ Values are the mean difference (95% CI); difference was calculated by subtracting the SAARD from the non–SAARD value.
§ Numbers of patients tested were 43 in the non–SAARD group and 128 in the SAARD group.

remained slow in both groups (*see* below). Adverse reactions occurred frequently in both therapeutic groups but were reversible in all cases. Our data therefore suggest that treatment of recent-onset rheumatoid arthritis with SAARDs suppresses disease activity more effectively than treatment with NSAIDs alone, at the expense of more frequent adverse effects.

For this study, we defined recent-onset rheumatoid arthritis as rheumatoid arthritis that had a disease duration of less than 1 year. Most patients were enrolled shortly after diagnosis, but the exact date of disease onset for each patient was not registered. This may be a limitation of our study, because other extraneous factors may confound the effects of therapy in patients who are at either extreme of the first year of disease. We feel, however, that it is difficult to reliably determine disease duration in these patients more precisely.

Patients in the non–SAARD group also showed improvement in disease activity. The change was greater for patients who discontinued the non–SAARD strategy than for those who continued the strategy. Despite the small numbers of patients in these non–SAARD subgroups, the differences were statistically significant. Nevertheless, clinical improvement in primary end points was found for many of the patients who continued the non–SAARD strategy. Therefore, despite the small number of complete remissions, NSAIDs clearly had a substantial beneficial effect in 25% to 50% of our patients with early rheumatoid arthritis. Identification of these patients would be useful, but, so far, convincing prognostic characteristics have not been found, and these could not be identified from the baseline values of this group. Previous investigations (36) have shown a placebo effect in treating rheumatoid arthritis, but we feel that the benefit of NSAIDs cannot be fully attributed to this effect.

Crossing over from NSAID therapy to treatment with a SAARD occurred increasingly during the study year, although most patients in the non–SAARD group could comply with their initially assigned treatment strategy. Crossing over in the non–SAARD group was usually done because NSAIDs were insufficiently effective, and more improvement was seen in patients who crossed over than in patients who continued to receive the non–SAARD strategy. Because our results are based on an intention-to-treat analysis, patients from the non–SAARD group who started to use a SAARD (or corticosteroid) were included in the comparative analysis, as were patients who used oral or intra-articular corticosteroids (use of the latter occurred more frequently in the non–SAARD group). The estimates of differences in effectiveness must therefore be considered conservative. Toxicity was the primary reason for discontinuation of treatment strategy in the SAARD group; nevertheless, 92% of patients were still receiving their assigned therapies at 12 months, and 81% were even receiving their initial SAARD. Toxicity in both groups should not be interpreted as indicative of differential adverse effects of SAARDs and NSAIDs, because NSAIDs were used in both groups, and it is often hard to distinguish whether adverse reactions in individual patients should be attributed to the SAARD or the NSAID.

The percentages of patients who continued to receive therapy are higher than those reported previously. Wolfe and colleagues (20) found that the 1-year "drug survival" rate for intramuscular gold, hydroxychloroquine, D-penicillamine, auranofin, and methotrexate ranged from 65% to 80% (20). In another study (37), the 12-month drug survival rate was 50% to 70% for hydroxychloroquine, intramuscular gold, D-penicillamine, and sulfasalazine. Drug survival rates might have been higher in our study because of the detailed guidelines we used for dose adjustment and discontinuation of therapy in case

Table 5. Changes from Baseline in the Non–SAARD Group and the SAARD Group: Secondary End Points*

Secondary End Points	Non–SAARD Group† (n = 57)	SAARD Group† (n = 181)	Difference‡
6 months			
Grip strength, *kPa*	+1 (−17, 19)	+8 (−11, 25)	−7 (−12 to −2)
Well-being score, *mm*	−17 (−47, 13)	−21 (−52, 10)	4 (−6 to 13)
Morning stiffness, *min*	−17 (−186, 152)	−68 (−225, 89)	51 (1 to 102)
C-reactive protein level, *mg/L*§	−7 (−36, 22)	−20 (−60, 20)	13 (−2 to 28)
Hemoglobin concentration, *mmol/L*	−0.1 (−0.9, 0.7)	+0.2 (−0.5, 0.9)	−0.3 (−0.5 to 0.0)
Platelet count, $\times 10^9$/*L*	−13 (−101, 75)	−49 (−138, 40)	36 (7 to 66)
12 months			
Grip strength, *kPa*	+3 (−17, 23)	+9 (−10, 28)	−6 (−12 to 0)
Well-being score, *mm*	−12 (−42, 18)	−21 (−52, 10)	9 (−1 to 18)
Morning stiffness, *min*	−37 (−159, 85)	−66 (−211, 79)	29 (−13 to 72)
C-reactive protein level, *mg/L*§	−5 (−42, 32)	−23 (−63, 17)	18 (3 to 32)
Hemoglobin concentration, *mmol/L*	0.0 (−0.8, 0.8)	+0.3 (−0,5 1.1)	−0.3 (−0.5 to 0.0)
Platelet count, $\times 10^9$/*L*	−15 (−110, 80)	−50 (−139, 39)	35 (7 to 64)

* Ranges for end point variables are as follows: grip strength, 0 to 120 kPa; well-being score, 0 to 100 mm; morning stiffness, 0 to 720 min. SAARD = slow-acting antirheumatic drugs.
† Values are the mean (−SD, +SD). Negative values indicate improvement for all outcome variables, with the exception of grip strength and hemoglobin concentration.
‡ Values are mean difference (95% CI); difference was calculated by subtracting the SAARD from the non–SAARD value.
§ The numbers of patients tested were 39 in the non–SAARD group and 107 in the SAARD group.

of adverse reactions. Furthermore, the setting of a clinical trial in which treatment discontinuation must be discussed with other rheumatologists and explained in the patient's record may enhance drug survival. This practice of applying strict rules for SAARD discontinuation might benefit nonstudy patients as well. Lack of long-term effectiveness has sometimes been attributed to short courses of second-line drugs imposed because of adverse reactions or impatience with delayed onset of action (20, 21).

Radiologic joint damage progressed in both treatment strategy groups but was worse in the non–SAARD than in the SAARD group. However, the difference represents only one erosion or one point for joint space narrowing. This is a minimal difference. Although the number of patients who did not have radiographs was high, it is unlikely that these missing values influenced our results. Characteristics at baseline did not differ between the two study groups for patients with missing radiographs, whose disease activity values were slightly worse in both groups. A 90% chance of finding this difference at the 5% level of significance would have required more than 500 patients in each group. Few clinical trials have been able to show that one of the available SAARDs can retard joint damage. In a review of the literature, Iannuzzi and coworkers (18, 19) concluded that no firm evidence indicates that any of the frequently used second-line antirheumatic drugs have this capability. In a few studies (38, 39), intramuscular gold injections have been found to retard radiologic progression. These findings might be explained partly by the fact that compliance is guaranteed in the case of intramuscular injections given by the physician, although the results of our study do not confirm this hypothesis. More recently, sulfasalazine was shown to decrease the rate of radiologic progression more than did hydroxychloroquine at 48 weeks in patients with early rheumatoid arthritis (31). In a meta-analysis (40), patients treated with methotrexate and patients treated with SAARDs other than methotrexate had similar rates of progression. In our study, early administration of second-line drugs did not reduce radiologic progression. The association between sustained inflammatory activity and subsequent radiologic damage that has been reported elsewhere (15, 16) suggests that statistically significant differences might arise in our patients after prolonged follow-up. However, if much of the joint damage occurs in the first years of the disease and the rate of progression has already decreased after 1 year (41, 42), then our 1-year comparison of radiologic damage in the two groups might be representative for subsequent years.

Thus, the superiority of the SAARD strategy over the non–SAARD strategy in suppressing disease activity is not reflected in the radiologic progression scores. The distinction between NSAIDs and SAARDs therefore cannot be based on the capacity of SAARDs to reduce anatomical damage in the first year after diagnosis of rheumatoid arthritis. Recently, a new classification has been proposed in which symptom-modifying antirheumatic drugs are distinguished from disease-controlling antirheumatic therapy (43, 44). Glucocorticosteroids, NSAIDs, and SAARDs are all considered to be symptom-modifying antirheumatic drugs because they have failed to control disease and provide long-term good health. However, because SAARDs clearly suppress disease activity more effectively than do NSAIDs alone, considering the two types of drugs together in one category seems unwarranted.

In conclusion, our results suggest that the early treatment of rheumatoid arthritis may be most effective when a SAARD is introduced immediately. Prolonged follow-up of our patients is needed to show the possible long-term consequences of this treatment strategy. To date, however, early administration of second-line drugs in rheumatoid arthritis seems warranted, given the more effective suppression of signs and symptoms of disease activity and overall toxicity that is at least as acceptable as that which accompanies NSAID therapy. Future studies on the effectiveness of treatment of early rheumatoid arthritis should no longer comprise groups treated with NSAIDs only.

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References

1. **Wilske KR, Healey LA.** Remodeling the pyramid—a concept whose time has come. J Rheumatol. 1989;16:565-7.
2. **Roth SH.** Rethinking rheumatic disease therapy [Editorial]. J Rheumatol. 1989;16:1408-9.
3. **Bensen WG, Bensen W, Adachi JD, Tugwell PX.** Remodelling the pyramid: the therapeutic target of rheumatoid arthritis [Editorial]. J Rheumatol. 1990;17:987-9.
4. **Hess EV, Luggen ME.** Remodeling the pyramid—a concept whose time has not yet come [Editorial]. J Rheumatol. 1990;16:1175-6.
5. **Kantor TG.** Order out of chaos—the primary mission of the pyramid [Editorial]. J Rheumatol. 1990;17:1580-1.
6. **Pincus T, Callahan LF.** Remodeling the pyramid or remodeling the paradigms concerning rheumatoid arthritis—lessons from Hodgkin's disease and coronary artery disease [Editorial]. J Rheumatol. 1990;17:1582-5.
7. **Fries JF.** Reevaluating the therapeutic approach to rheumatoid arthritis: the sawtooth strategy. J Rheumatol. 1990;22:12-5.
8. **Wilske KR, Healey LA.** Challenging the therapeutic pyramid: a new look at treatment strategies for rheumatoid arthritis. J Rheumatol. 1990;25:4-7.
9. **Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al.** The mortality of rheumatoid arthritis. Arthritis Rheum. 1994;37:481-94.
10. **Rasker JJ, Cosh JA.** Course and prognosis of early rheumatoid arthritis. Scand J Rheumatol Suppl. 1989;79:45-56.
11. **Scott DL, Symmons DP, Coulton BL, Popert AJ.** Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet. 1987;1:1108-11.
12. **Wolfe F.** 50 years of antirheumatic therapy: the prognosis of rheumatoid arthritis. J Rheumatol Suppl. 1990;22:24-32.
13. **Brook A, Corbett M.** Radiographic changes in early rheumatoid disease. Ann Rheum Dis. 1977;36:71-3.
14. **Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T.** Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol. 1989;16:585-91.
15. **van Leeuwen MA, van der Heijde DM, van Rijswijk MH, Houtman PM, van Riel PL, van de Putte LB, et al.** Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. J Rheumatol. 1994;21:425-9.
16. **Möttönen TT.** Prediction of erosiveness and rate of development of new erosions in early rheumatoid arthritis. Ann Rheum Dis. 1988;47:648-53.
17. **Fries JF.** Safety issues related to DMARD therapy. J Rheumatol Suppl. 1990; 25:14-7.
18. **Kushner I.** Does aggressive therapy of rheumatoid arthritis affect outcome? J Rheumatol. 1989;16:1-4.
19. **Iannuzzi L, Dawson N, Zein N, Kushner I.** Does drug therapy slow radiographic deterioration in rheumatoid arthritis? N Engl J Med. 1983;309:1023-8.
20. **Wolfe F, Hawley DJ, Cathey MA.** Termination of slow-acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol. 1990;17:994-1002.
21. **Capell HA, Brzeski M.** Slow drugs: slow progress? Use of slow acting antirheumatic drugs (SAARDs) in rheumatoid arthritis. Ann Rheum Dis. 1992; 51:424-9.
22. **Jaffe IA.** Combination therapy of rheumatoid arthritis—rationale and overview. J Rheumatol Suppl. 1990;25:24-7.
23. **Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al.** The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
24. **van der Heide A, Jacobs JW, Dinant HJ, Bijlsma JW.** The impact of endpoint measures in rheumatoid arthritis clinical trials. Semin Arthritis Rheum. 1992;21:287-94.
25. **Fries JF, Spitz P, Kraines RG, Holman HR.** Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137-45.
26. **Bijlsma JW, Oude Heuvel CH, Zaalberg A.** Development and validation of the Dutch questionnaire capacities of daily life (VDF) for patients with rheumatoid arthritis. J Rehabil Sci. 1990;3:71-4.
27. **van der Heide A, Jacobs JW, van Albada-Kuipers GA, Kraaimaat FW, Geenen R, Bijlsma JW.** Self report functional disability scores and the use of devices: two distinct aspects of physical function in rheumatoid arthritis. Ann Rheum Dis. 1993;52:497-502.
28. **Thompson PW, Silman AJ, Kirwan JR, Currey HL.** Articular indices of joint inflammation with rheumatoid arthritis. Correlation with the acute-phase response. Arthritis Rheum. 1987;30:618-23.
29. **van den Brink HR, van der Heide A, Jacobs JW, van der Veen MJ, Bijlsma JW.** Evaluation of the Thompson articular index. J Rheumatol. 1993; 20:28-32.
30. **Sharp JT, Young DY, Bluhm GB, Brook A, Brower AC, Corbett M, et al.** How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum. 1985;28:1326-35.
31. **van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB.** Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet. 1989;1:1036-8.
32. **Goldsmith CH, Boers M, Bombardier C, Tugwell P.** Criteria for clinically important changes in outcomes: development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. OMERACT Committee. J Rheumatol. 1993;20:561-5.
33. **Scott DL, Spector TD, Pullar T, McConkey B.** What should we hope to achieve when treating rheumatoid arthritis? Ann Rheum Dis. 1989;48:256-61.
34. **Rothman KJ.** No adjustments are needed for multiple comparisons. Epidemiology. 1990;1:43-6.
35. **Norusis MJ.** SPSS/PC+™ Base Manual. Chicago: SPSS, Inc.; 1988.
36. **Williams HJ, Ward JR, Dahl SL, Clegg DO, Willkens RF, Oglesby T, et al.** A controlled trial comparing sulfasalazine, gold sodium thiomalate, and placebo in rheumatoid arthritis. Arthritis Rheum. 1988;31:702-13.
37. **Wijnands MJ, van't Hof MA, van Leeuwen MA, van Rijswijk MH, van de Putte LB, van Riel PL.** Long-term second-line treatment: a prospective drug survival study. Br J Rheumatol. 1992;31:253-8.
38. **Sigler JW, Bluhm GB, Duncan H, Sharp JT, Ensign DC, McCrum WR.** Gold salts in the treatment of rheumatoid arthritis. A double-blind study. Ann Intern Med. 1974;80:21-6.
39. **Luukkainen R.** Chrysotherapy in rheumatoid arthritis with particular emphasis on the effect of chrysotherapy on radiographical changes and on the optimal time of initiation of therapy. Scand J Rheumatol Suppl. 1980;34:1-56.
40. **Alarcón GS, López-Méndez A, Walter J, Boerbooms AM, Russell AS, Furst DE, et al.** Radiographic evidence of disease progression in methotrexate treated and nonmethotrexate disease modifying antirheumatic drug treated rheumatoid arthritis patients: a meta-analysis. J Rheumatol. 1992;19: 1868-73.
41. **Eberhardt KB, Rydgren LC, Pettersson H, Wollheim FA.** Early rheumatoid arthritis—onset, course, and outcome over 2 years. Rheumatol Int. 1990; 10:135-42.
42. **van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, van 't Hof MA, van Rijswijk MH, et al.** Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum. 1992;35:26-34.
43. **Paulus HE, Scott DL, Edmonds JP.** Classification of antirheumatic drugs. A new proposal. Arthritis Rheum. 1992;35:364-5.
44. **Edmonds JP, Scott DL, Furst DE, Brooks P, Paulus HE.** Antirheumatic drugs: a proposed new classification [Editorial]. Arthritis Rheum. 1993;36: 336-9.